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14. ABSTRACT The goals of this synergistic grant proposal are to develop computational and biological tools to investigate the relationship between mammographic density and short-term breast cancer risk. Here we have worked to correlate computational models of mammographic and stromal patterning with clinical outcome leading to the construction of multi-disciplinary tools for the classification of breast cancer risk and response to prevention strategies. To this end we have currently evaluated mammographic density in 25 women taking tamoxifen chemoprevention and 25 high-risk women who elected not to take tamoxifen using pattern analysis of 1) serial mammograms, 2) serial breast Magnetic Resonance Imaging, and 3) Random Periareolar Fine Needle Aspiration (RPFNA). We observe no correlation between the presence or absence of atypia after tamoxifen prevention and changes in mammographic density. Two women developed breast cancer while taking tamoxifen who had a progressive decrease in mammographic density. These findings demonstrate the viability of using RPFNA to assess prevention response.					
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INTRODUCTION:

Mammographic density serves as independent marker of short term breast cancer risk and a surrogate marker of response to a variety of prevention agents¹⁻³. Although a majority of breast cancers are epithelial in origin, there is evidence that stromal content of the breast is an important predictor of mammographic density. There is increasing evidence that the stroma plays a role in breast cancer initiation⁴. However, currently we lack an understanding of how mammographic density is affected by the individual contribution of epithelial and stromal components and the biological potential of stromal and/or epithelial cells. The goals of this synergistic grant proposal are to develop computational and biological tools to investigate the relationship between mammographic density, stromal content of the breast, and the role of stromal/epithelial interactions in regulating proliferation, and ultimately, short-term breast cancer risk. To achieve these goals we bring together investigators with expertise in mathematical fractal pattern assessment, 3-D models of stromal/epithelial interactions, and clinical breast cancer risk assessment. Together we propose to correlate computational models of mammographic and stromal patterning with biological assays of stromal/epithelial proliferation, and clinical outcome leading to the construction of multi-disciplinary tools for the classification of breast cancer risk and response to prevention strategies.

Random Periareolar Fine Needle Aspiration (RPFNA) is a research technique that has been prospectively validated to assess 1) short-term breast cancer risk and 2) response to chemoprevention in high-risk women⁵⁻⁷. While RPFNA was originally developed to evaluate early epithelial changes, RPFNA also provides a representative sampling of stromal cells in high-risk women. prevention agents, and therefore, mammographic In this Synergy Proposal, we are currently testing the *hypothesis* that in women with epithelial atypia, 1) mammographic and stromal patterning does not consistently predict the degree of epithelial atypia (measured by Masood Cytology Index) and 2) mammographic density may not be a reliable measure of epithelial response to prevention agents.

BODY:

Objective 1: To investigate the relationships between mammographic density, mammary stromal patterns and computational image analysis of the breast. The goals of this aim are to 1) Quantitate the stromal-epithelial cell ratios obtained from RPFNA and quantitate imaged breast density computer modeling; 2) Perform comparisons and correlations between RPFNA stromal-epithelial cell ratios, and mammographic density; 3) Statistically examine the relationship between mammographic density, MRI fibroglandular volume, and RPFNA stromal to epithelial composition and stromal patterning.

Task 1: RPFNA, Digitizing, Annotation, and Posting.

TIMELINE: Years 1-2: 50 RPFNA will be performed in high-risk women, slides will be prepared, cytology assessed, slides will be digitized, annotated and posted.

MILESTONES: Year 1: 50 RPFNA performed, tested, and posted.

RPFNA is a research technique that has been prospectively validated to assess 1) short-term breast cancer risk and 2) response to chemoprevention in high-risk women⁵⁻⁷. RPFNA cytology is assessed by Masood score by a single dedicated pathologist (*Carola Zalles*) who has >10 years experience in assessing RPFNA cytology⁵⁻⁷. This allows for reproducible identification of early cytological changes in mammary epithelial cells. Epithelial and stromal cells are counted in 4 individuals RPFNA slides.

Cellular morphology	Cellular pleomorphism	Myoepithelial cells	Aniso-nucleosis	Nucleoli	Chromatin clumping	Score
Monolayer	Absent	Many	Absent	Absent	Absent	1
Nucl. overlap	Mild	Moderate	Mild	Micro-nucleoli	Rare	2
Clustering	Moderate	Few	Moderate	Micro-nucleoli	Occasional	3
Loss cohesion	Conspicuous	Absent	Frequent	Macro-nucleoli	Frequent	4

Masood scores: 6-10 Normal; 11-13 Hyperplasia; 14-15 Atypia; 16-17 High-grade atypia; >17 Suspicious for cancer.

We performed serial RPFNA on 25 high-risk women and 25 high-risk women taking tamoxifen chemoprevention. Women not taking tamoxifen were risk-matched to the 25 women who took tamoxifen. Each woman underwent an average of 4.4 RPFNA. A total of 228 RPFNA were analyzed. Subject demographics are presented in **Table 1**. All 228 RPFNA slides have been digitized, annotated, on a password protected server.

The average time of total observation for women was 33 months (range 18 to 54 months) and the average time on tamoxifen prevention was 22 months (range 12 to 48 months). The average age of women was 46 (range 40 to 52). Eighty percent of women were premenopausal and 20% were either perimenopausal or postmenopausal. Twenty percent of women were African American and 80% were Caucasian. See **Table 1** for subject demographics.

We previously used RPFNA to test for cytological response to tamoxifen chemoprevention in high-risk women with atypia. We observed that disappearance of atypia occurs within the first 12 months of initiating tamoxifen. (**Figure 1**). After 12 months, women do not have disappearance of atypia. In the 25 women taking tamoxifen chemoprevention in this study, we observe that 14/25 women have disappearance of atypia after 12 months tamoxifen prevention and 11 women have persistent atypia. This is consistent with the Breast Cancer Prevention Trial (P1) which demonstrated a 50% reduction in estrogen receptor-positive breast cancer.

Task 2: Analysis of Epithelial/Stromal Counts.

TIMELINE: Years 1-2: Cytological Quantization: Using a standard volume of suspended RPFNA cells, four cytology slides will be generated. Epithelial cell and stromal cell counts will be quantitated by a blinded cytologist in triplicate.

Computational Pattern Analysis: Fractal pattern analysis of epithelial and stromal cells will be performed on digitized images of fixed cell slides from the RPFNA.

MILESTONES: Year 1: Stromal and Epithelial Cell Counts will be tested from 50 subjects using cytological quantitation, biochemical and computational pattern analysis.

Epithelial/Stromal Counts: We performed epithelial cell counts on a standard volume of RPFNA cells from 228 RPFNA slides from 50 subjects described above in **Task 1**. Total cell counts are determined from all RPFNA slides. Stromal cell counts and computational analysis is on-going. We observed a correlation between a decrease in cell counts and the presence or absence of atypia after 12 months tamoxifen chemoprevention ($p < 0.001$). Of the 14 women who had disappearance of atypia all had $>75\%$ decrease in RPFNA cell counts. For the 11 women who had persistent atypia, no subject had a $>25\%$ decrease in cell counts after 12 months tamoxifen prevention.

Task 3: Analysis of Mammographic Density:

TIMELINE: Year 1-2: Mammographic density will be assessed quantitatively using 1) visual assessment of mammographic density and 2) a novel automated computer method

MILESTONES: Year 2: 100 Mammograms analyzed by visual assessment and computer automated methods. A total of 250 (150 old; 100 new) will be completed.

Mammographic Density: Over 475 serial screen-film mammograms were digitized from the 50 women described in **Task 1**: 25 high-risk women taking tamoxifen prevention and 25 high-risk women who elected not to take tamoxifen. Woman had an average of 4.3 mammographic determinations. Mammograms from both breasts were digitized, including cranial caudal and medial lateral views.

Over 475 serial screen-film mammograms were digitized from 25 women taking tamoxifen prevention and 25 controls using a new Howtek MultiRad 860 digitizer. The anonymized mammographic images were stored on our private computer network and referenced in the database. Mammographic density was assessed quantitatively using established computer modeling techniques. We are using the public Digital Database for Screening Mammography. To verify the reproducibility and robustness with respect to imaging technique,

mammographic density we compared the medio-lateral oblique and craniocaudal views of the same digitized breast.

We find in the course of this analysis that assessment of mammographic breast density by analysis of films suffers from variability. **Figure 2** depicts a breast mammogram that was obtained in the same person on the same day. In order to effectively and consistently analyze mammographic density, we are currently using breast MRI to assess breast density.

Task 4: Analysis of MRI

TIMELINE: Year 1-2: MRI slices will be segmented manually and total voxel volumes for the fibroglandular tissue will be computed over the whole breast. Patterns of suspicious MRI signal enhancement will be preliminarily evaluated.

MILESTONES: Year 2: Analysis of 100 MRIs will be completed. A total of 250 (150 old; 100 new) will be completed.

MRI Image Analysis is ongoing to evaluate breast density. MRI differentiates fatty and fibroglandular tissue with high precision and accuracy, therefore allowing a different assessment breast density^{8,9}. We performed and collected an average of 3.1 breast MRI on each of our 50 subjects that are described in **Task 1**. All MRI were performed with a commercial system using a dedicated breast coil. The digital files were obtained from the Picture Archiving and Communication System (PACS) and placed on our private computer network for the specified analysis. We are currently performing a preliminary semi-automatic analysis of the 3-D MRI images. MRI slices are segmented manually and total voxel volumes for the fibroglandular tissue are computed over the whole breast. Patterns of suspicious MRI signal enhancement are present in 7/50 subjects and are preliminarily evaluated.

Breast MRI detected 4 breast cancers in the 50 subjects described in **Task 1**. All four subjects had a decrease in mammographic density. Analysis of density by breast MRI in these subjects is on-going.

Task 5: Statistical analysis

TIMELINE: Years 1-2: Statistical analysis will be performed to correlate mammographic density with, MRI patterning, stromal cell counts, and stromal patterning.

MILESTONES: Year 2: Statistical analysis will be completed.

Statistical Analysis: Statistical comparison are on-going and methods include, 1) Pearson's correlation coefficient, 2) Spearman rank correlation coefficient, and 3) mutual information. *Pearson's correlation coefficient* measures linear dependence between random variables. *Spearman rank correlation coefficient*¹⁰ can show correlation between rank-ordered data. Since the data is ranked, 1) the values are not used directly; 2) the measure of correlation is independent of scales; 3) no assumptions are made about the distribution of the underlying data. *Mutual information*^{11,12} is a method for measuring the general statistical dependence between random variables. Mutual information will be computed to test whether a more general statistical dependence exists between mammographic density, fractal patterning, and stromal/epithelial counts. Questions that we are currently testing include:

a) Do stromal and/or epithelial counts predict mammographic density? We predict that stromal cell counts and the stromal/epithelial ratio will be the primary predictor of mammographic density.

Observation to date: We have completed this analysis for 50 subjects and observe that epithelial counts do not predict mammographic density. We observe a direct correlation between epithelial cell counts and Masood Cytology abnormalities ($p < 0.001$). Stromal cell counts are in process.

b) Is there a correlation between the presence or absence of atypia after tamoxifen chemoprevention and changes in mammographic density? We predict that there will not be a correlation.

Observation to date: We tested for a correlation in the 25 subjects described in **Task 1** who took tamoxifen chemoprevention. There was no correlation ($p>0.5$) when the data analysis was performed for individual women or individual breasts (**Figures 3 and 4**). Two women developed breast cancer while taking tamoxifen chemoprevention. One woman is depicted in **Figure 5**. Both women had a decline in mammographic density. In contrast, a minority of women had correlation between mammographic density and disappearance of atypia in RPFNA. An example is depicted in **Figure 6**.

c) Is there a correlation between mammographic density, mammographic and stromal fractal patterning, and RPFNA Masood epithelial cytology? We predict that in subjects with hyperplasia (vs. non-proliferative cytology) there will be a direct relationship, however, in subjects with atypia there will not be a direct correlation. These studies will provide rational for developing multi-modality measures of short-term breast cancer risk and response to prevention strategies.

Observation to date: These studies have been initiated and are on-going.

OBJECTIVE 2: To test whether increased mammographic density correlates with increased stromal proliferation. To accomplish this aim we are using combinations of 1) defined epithelial cell and 2) patient-derived epithelial cells obtained RPFNA will be co-cultured with stroma isolated from subjects with high- and normal-mammographic density. Co-culture methods will include 3-D culture and 3-D rotary bioreactor culture, stromal and epithelial cells will be tested for proliferation and transcriptional activation.

Task 1: Isolation of Mammary Stromal and Epithelial Cells from RPFNA

TIMELINE: Years 1-2: Obtain matched HMECs and stromal cells from high-risk patients with high and low-medium mammographic density.

MILESTONES: Year 2: Obtain 10 matched sets of stroma and epithelial cells from RPFNA.

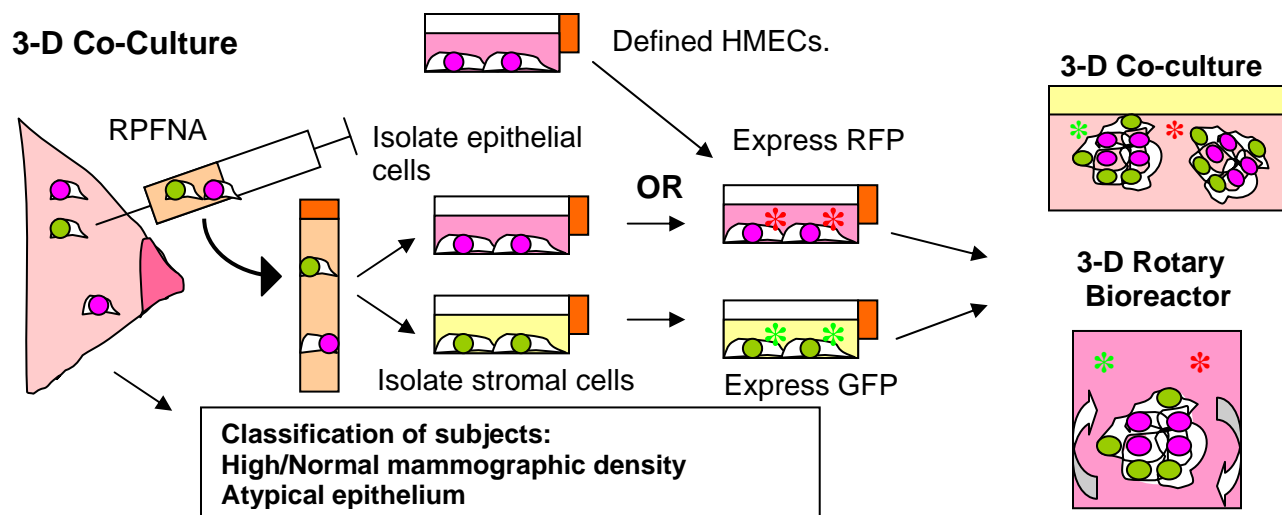
Observations to date: We have collected matched HMECs and stroma from 5 high-risk patients with high mammographic density.

Task 2: Epithelial/Stromal Co-Culture.

TIMELINE: Years 1-2: Perform 3-D culture with combinations of stroma and epithelial cells obtained from women with high and low-medium mammographic density.

MILESTONES: Year 1: 3-D culture performed on 5-10 samples.

We initiated co-culture of defined and patient-derived epithelial/stroma cells. Cells have been isolated from high-risk women with 1) atypia who have 2) high or normal mammographic density. Co-culture methods include 3-D bioreactor culture. We are currently testing for dominance of stroma versus epithelium using the strategy outlined below.



Task 4: Statistical analysis correlating stromal proliferation with mammographic density and breast stromal composition.

TIMELINE: *Year 2:* Statistical analysis will be performed.

MILESTONES: *Year 2:* Statistical analysis will be completed.

Results to date: Not yet initiated. Will be initiated in Year 2.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- 1) RPFNA is a viable means to track response to chemoprevention in high-risk women with mammary atypia.
- 2) Disappearance or persistence of atypia in RPFNA cytology in women taking 12 months of tamoxifen prevention does not correlate with changes in mammographic density.
- 3) Breast Magnetic Resonance Imaging appears to be a more reliable measure of breast density than film determination of mammographic density.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes from this proposal:

1) Manuscripts

Lo, J, Barron, A, and Seewaldt, VL. Presence or absence of atypia in RPFNA does not correlate with mammographic density changes after 12 months tamoxifen prevention. In preparation.

2) Presentations

Lo, J, Barron, A, and Seewaldt, VL. Presence or absence of atypia in RPFNA does not correlate with mammographic density changes after 12 months tamoxifen prevention. Presented *Era of Hope*, June 2008.

3) Funding

CALGB multi-institutional trial to test for correlation between mammographic density, MRI determined breast density, and RPFNA cytology. Concept submitted (Seewaldt)

R01 RFA Biology of Premalignancy. Submitted (Seewaldt).

K01 Career Development Award, Submitted (Ibarra PI, Seewaldt Mentor).

4) Training

Graduate student Nicholas D'Amato, DoD Predoctoral Award.

Postdoctoral student Julie Ostrander, DoD Multi-Disciplinary Award.

Junior Faculty, Catherine Ibarra, K01 award.

CONCLUSIONS:

a) RPRFNA epithelial counts do not predict mammographic density. Stromal cell counts and the stromal/epithelial ratio appear to be the primary predictor of mammographic density.

b) Persistence or absence of atypia in RPFNA cytology after 12 months tamoxifen prevention do not predict changes in mammographic density.

“So what”:

To our knowledge, this is the first study to attempt to develop a computational model of mammographic density and correlate this model with stromal/epithelial biology. This project provides a rapid means to test for response to prevention and a new method to test for breast cancer risk. The innovative aspect of this work is that we are testing our observations in mammary stroma and epithelium directly isolated from high-risk women at the earliest stages of mammary carcinogenesis. These studies have created a unique interdisciplinary database of cytology, histology, genetic and cellular information for women at high-risk of developing breast cancer.

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APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

See below.

	High-risk subjects NOT on tamoxifen prevention	High-risk subjects on tamoxifen prevention	Total subjects
Number	25	25	50
Average Age	41 (41-48)	40 (40-52)	46 (40-52)
Menopausal status			
Premenopausal	19/25	21/25	40/50 (80%)
Perimenopausal	6/25	4/25	10/50 (20%)
Race			
Caucasian	21/25	19/25	40/50 (80%)
African American	4/25	6/25	10/50 (20%)
Risk			
Atypia/LCIS	19/25	19/25	38/50 (76%)
DCIS	6/26	6/25	12/50 (24%)
Time of observation	30 mos (18 to 50 mos)	31 mos (18 to 54 mos)	31 mos (18 to 54 mos)
Duration of tamoxifen	n/a	22 mos (12 to 48 mos)	n/a
Average density			
Average mammographic density	57% (range 31% to 55%)	54% (range 34% to 67%)	55% (range 31% to 67%)
Average number of RPFNA	4.5	4.6	4.4 (3-6 RPFNA)
RPFNA change			
Disappearance of atypia	1/25	14/25	15/50
Persistence of atypia	24/25	11/25	35/50
Development of breast cancer	2	2	4

Table 1: Demographic information of women participating in this analysis. Abbreviations: LCIS (lobular carcinoma in situ), DCIS (ductal carcinoma in situ); RPFNA (Random Periareolar Fine Needle Aspiration). Subjects not taking tamoxifen prevention were selected to risk-match subjects taking tamoxifen prevention.

Figure 2\1: Time line for estimating response to tamoxifen prevention. We tested for the time on tamoxifen to determine persistent atypia versus disappearance of atypia. Women did not have disappearance of atypia after undergoing 12 months of tamoxifen prevention. Therefore, women were judged to have persistent atypia if they had atypia after receiving 12 months tamoxifen prevention.

Fig. 1 RPFNA pre/post tamoxifen

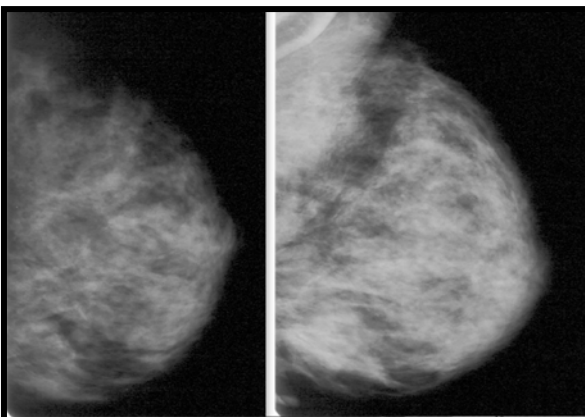
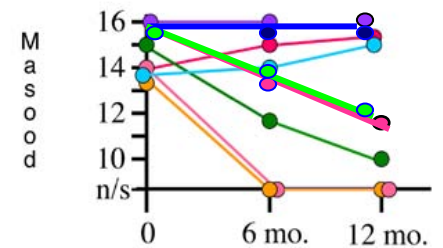


Figure 2: Mammographic assessment of the same subject utilizing the same breast, same machine, same mammographer. The two mammograms demonstrate significant differences in mammographic density (65% versus 84% density). Differences in mammographic density can be accounted for due to potential differences in positioning, film processing, radiographic technique, and compression. These film images illustrate the inherent difficulties in estimating mammographic density based on film images.

Is disappearance of atypia in RPFNA predicted by decrease in mammographic density (Women)

Mammographic density declines $\geq 15\%$ from baseline
Absence of atypia in RPFNA >12 mos after start Tam

$p > 0.50$

		Disappearance of atypia in RPFNA		
		Yes	No	
$\geq 15\%$ decrease density	Yes	6	5	11
	No	8	8	16
		14	11	25

Figure 3: Is disappearance of atypia in RPFNA predicted by a decrease in mammographic density? Data is analyzed based on individual women.

Is disappearance of atypia in RPFNA predicted by decrease in mammographic density (BREAST)

Mammographic density declines $\geq 15\%$ from baseline
Absence of atypia in RPFNA >12 mos after start Tam

$p > 0.5$

		Disappearance of atypia in RPFNA		
		Yes	No	
$\geq 15\%$ decrease density	Yes	9	6	15
	No	13	16	29
		22	22	44

Figure 4: Is disappearance of atypia in RPFNA predicted by a decrease in mammographic density? Data is analyzed based on individual breasts.

Figure 5: Example of discordance between mammographic density and tamoxifen prevention in a subject with a history of contralateral ductal carcinoma in situ (right breast). The subject had a significant decrease in mammographic density in the left breast but had persistent atypia in the left breast after > 12 months tamoxifen prevention. She also developed breast cancer in the right breast at 42 months as depicted in the below breast magnetic resonance imaging (MRI).

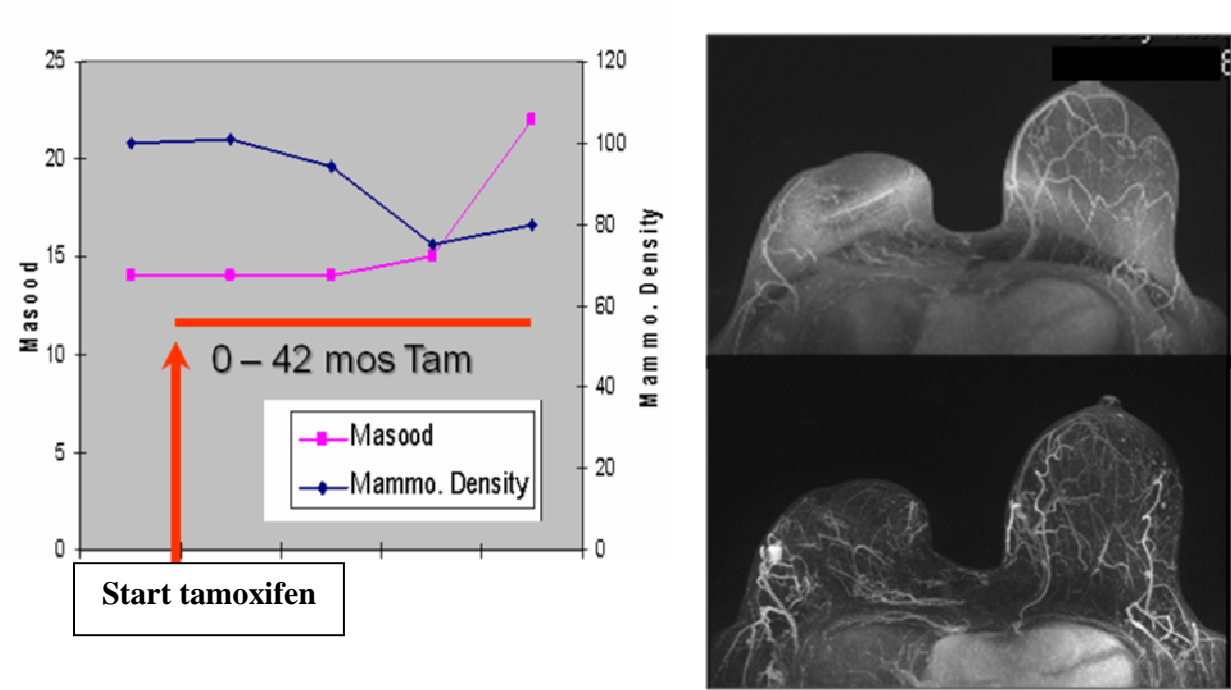


Figure 6: Example of concordance between mammographic density and RPFNA cytology in a high-risk woman with a history of excisional biopsy demonstrating atypical hyperplasia.

